

Low-dose prostaglandin E1 usage in term newborns with duct-dependent congenital heart disease

PGE1 use in duct-dependent heart disease

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Abstract

Aim: This study aimed to investigate the usage and effects of low-dose Prostaglandin E1 in term newborns diagnosed with duct-dependent congenital heart disease.

Materials and Methods: The study was conducted retrospectively on term cases diagnosed with duct-dependent congenital heart disease monitored in the pediatric cardiac intensive care unit between January 1, 2022, and January 1, 2024. The usage and effects of low-dose Prostaglandin E1 applied according to our clinical protocol were evaluated in the cases. The results were analyzed statistically.

Results: There were 235 cases (57% male) during the study period. The median weight was 2950 grams (IQR 2800-3100 grams), and the median gestational age was 39 weeks (IQR 38-40 weeks). There were systemic-dependent CHD (n = 91), pulmonary-dependent CHD (n = 102), and mixing CHD (n = 42) cases. The median duration of PGE1 usage was 6 days (IQR 5-7 days). While the maintenance dose according to our clinical protocol was 0.005, dose escalation was observed in 20/91 (22%) systemic-dependent cases, 14/102 (13.7%) pulmonary-dependent cases, and 4/42 (9.5%) mixing cases ($p < 0.05$). Edema was observed in 38 cases (16.1%), hyperthermia in 31 cases (13.1%), gastrointestinal problems in 31 cases (13.1%), and apnea in 17 cases (7.2%).

Discussion: Low-dose PGE1 usage in term newborns diagnosed with duct-dependent congenital heart disease has been effective in maintaining duct patency. The usage of low-dose PGE1 resulted in a decrease in adverse effects compared to the reported rates in the literature.

Keywords

newborn, congenital heart disease, prostaglandin E1

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Introduction

Congenital heart disease (CHD) has a prevalence ranging from 4 to 8 per 1000 live births and represents a significant health issue for term infants. Critical CHD is a major cause of low cardiac output requiring surgical or catheter intervention within the first year of life, comprising approximately 15-25% of infants with CHD [1].

Duct-dependent congenital heart disease (DD-CHD) consists of cardiac lesions requiring a patent ductus arteriosus (PDA) for pulmonary or systemic blood flow. Infants with DD-CHD may develop cyanosis/hypoxia or decreased perfusion within hours or days after birth due to the closure of the PDA [2]. Based on their anatomical features and treatment approach, DD-CHD infants are categorized into three distinct groups: those dependent on systemic blood flow (such as aortic stenosis, interrupted aortic arch, hypoplastic left heart syndrome), those dependent on pulmonary blood flow (including pulmonary atresia, Tetralogy of Fallot, critical pulmonary stenosis, Ebstein anomaly), and those requiring adequate mixing (such as transposition of the great arteries) [1,3].

Prostaglandin E1 therapy is a well-known effective method for maintaining ductal patency in term infants with duct-dependent congenital heart disease (DD-CHD). In patients with DD-CHD, the administration of prostaglandin E1 (PGE1) helps preserve medical palliative shunting until an interventional procedure can be performed. However, prostaglandin E1 therapy poses specific challenges in the management of these patients. Apnea, hypoventilation, hypotension, vasodilation, flushing, diarrhea, seizures, and hyperpyrexia have been reported as common side effects of short-term, standard-dose prostaglandin E1 therapy [4-6].

The original dosage recommendation for Prostaglandin E1 was initially in the range of 0.05-0.10 µg/kg/minute, with subsequent reduction of the maintenance dose to 0.025 µg/kg/minute. Since the official approval of Prostaglandin E1, several studies have investigated the effectiveness of lower maintenance dose regimens. However, it is not yet clear how low the dose can be while maintaining ductal patency or how low it should be to minimize side effects [7].

In this study, we aimed to evaluate the effectiveness and side effect profile of Prostaglandin E1 at the starting dose of 0.01 µg/kg/minute and maintenance dose of 0.003-0.005 µg/kg/minute, which is our institutional protocol that has been implemented for a long time.

Materials and Methods

This study was conducted retrospectively on term cases diagnosed with duct-dependent congenital heart disease and followed in the pediatric cardiac intensive care unit between January 1, 2022, and January 1, 2024. In accordance with our clinical practice, Prostaglandin E1 was administered at a starting dose of 0.01 µg/kg/minute and a maintenance dose of 0.003-0.005 µg/kg/minute.

Patients with critical CHD who started prostaglandin E1 intake after the age of fourteen days, received prostaglandin E1 for more than 24 hours at another center, had a total dose duration of less than 12 hours, were born with a closed ductus arteriosus, and were diagnosed with heterotaxy syndrome, as well as

those with severe neurological disorders such as trisomy 13 and 18, were excluded from the study. The study was planned in accordance with the Helsinki Declaration after obtaining approval from the local committee.

Gestational age of 37 weeks or more was defined as full-term. Newborns with ductal dependent-CHD were grouped into three categories: (i) duct dependent pulmonary circulation (e.g., pulmonary atresia and tetralogy of Fallot), (ii) duct dependent systemic circulation (e.g., hypoplastic left heart syndrome, coarctation of aorta, and interruption of the aortic arch), (iii) duct dependent without an adequate mixing of blood between the two circulations (e.g., transposition of the great arteries) [3]. Echocardiograms, surgical, and catheterization reports were utilized to establish the final diagnosis and categorize patients into groups.

Demographic and clinical data were collected from medical records. Patient demographic data were collected, including gestational age, birth weight, diagnosis of CHD, and prenatal diagnosis. The total duration and dosage of PGE1 administration were recorded. Adverse effects were divided into groups as follows [8].

-Gastrointestinal: feeding intolerance (gastrointestinal reflux, vomiting, and residues over 25% of feed), number of feeding cessations during the infants' hospital stay, necrotizing enterocolitis (NEC, stage 2 and over according to Bell's criteria, diarrhea, and gastric antral mucosal hypertrophy [9].

-Cardiovascular: edema, flushing, heart failure, arrhythmia, bradycardia < 100 bpm, tachycardia > 180 bpm, and hypotension requiring medical treatment.

- Miscellaneous: hyperthermia (defined as body temperature > 37.5 °C, apnea, bleeding, seizure, jitteriness.

The data were analyzed using SPSS Statistics 21. The demographic data were presented as the number, percentage, and median (interquartile range (IQR)). Differences among categorical variables were tested via Pearson's chi-squared or Fisher's exact test. Differences among means between normally distributed continuous variables were evaluated with Student's t-test or analysis of variance. Differences among medians between continuous variables with non-parametric distribution were evaluated with the Mann-Whitney U-test or Kruskal-Wallis test. Both univariate and multivariate logistic regression were utilised to compare predictor variables with dichotomous categorical outcome variables. P values of <.05 were considered statistically significant.

Ethical Approval

This study was approved by the Ethics Committee of Basaksehir Cam ve Sakura City Hospital (Date: 2025-08-08, No: 316).

Results

During the study period, there were 235 cases (57% male) available. Of these, 91 cases had systemic-dependent CHD, 102 cases had pulmonary-dependent CHD, and 42 cases had mixing CHD. The specific CHD diagnoses and general characteristics of the cases are shown in Table 1.

The median weight was 2950 grams (IQR 2800-3100 grams), and the median gestational age was 39 weeks (IQR 38-40 weeks). The median duration of PGE1 usage was 6 days (IQR 5-7 days). While the maintenance dose according to our clinical

protocol was 0.005, dose escalation was observed in 20 out of 91 systemic-dependent cases, 14 out of 102 pulmonary-dependent cases, and 4 out of 42 mixing cases ($p < 0.05$). The clinical and general characteristics of the cases are shown in Table 2. PGE1 usage continued for more than 30 days in three cases diagnosed with hypoplastic left heart syndrome. A greater proportion of patients with systemic obstruction (20/91, 22%) required a dose increase than those with pulmonary obstruction (14/102, 13.7%, $p = 0.03$). Additionally, patients with dose escalation had significantly longer treatment times with prostaglandin E1, with a median of 225 hours compared with 127 hours for those without dose escalation ($p = 0.004$). Univariate ($p = 0.005$, odds ratio 1.09, 95% confidence interval 1.006–1.012) and multivariate ($p = 0.008$, odds ratio 1.006, 95% confidence interval 1.004–1.008) logistic regression also identified a statistically significant association between dose escalation and each additional hour of prostaglandin E1

Table 1. Specific cardiac diagnoses

Obstruction to systemic blood flow, n = 91 (n)	Obstruction to pulmonary blood flow, n = 102 (n)	Inadequate mixing, n = 42 (n)
Coarctation or aortic arch hypoplasia (35)	Critical PS (14)	TGA(42)
HLHS or HLHS variant(34)	VSD with PA (26)	
Interrupted aortic arch (12)	PA with IVS (14)	
Critical aortic stenosis (6)	TOF with PS (18)	
RV-dominant unbalanced AV canal (4)	DORV with PS/PA (10)	
	Ebstein anomaly (4)	
	Tricuspid atresia (10)	
	Other (6)	

AV = atrioventricular; DORV = double-outlet right ventricle; HLHS = hypoplastic left heart syndrome; IVS = intact ventricular septum; PA = pulmonary atresia; PS =pulmonary stenosis; RV = right ventricle; TGA = transposition of the great arteries; TOF = tetralogy of Fallot; VSD = ventricular septal defect

Table 2. Demographics and clinical characteristics by lesion category

Variables	Obstruction to systemic blood flow, n = 91	Obstruction to pulmonary blood flow, n = 102	Inadequate mixing, n = 42	p
Male sex	50(55)	60(59)	25(60)	NS
Median birth weight kg	2.9(2.7-3.1)	3(2.8-3.2)	2.9(2.8-3)	NS
Median gestational age weeks	38(37-39)	39(38-40)	38(37-39)	NS
Cesarean section	50(55)	63(61)	24(57)	NS
Prenatal diagnosis	54(59)	48(47)	30(71)	NS
Median PGE1 treatment time hours	150(130-165)	140(125-160)	96(80-120)	NS
Dose increased	20(22)	14(13.7)	4(9.5)	0.03
Mortality	14(15.3)	10(9.8)	4(9.5)	NS
n (%), median (IQR) NS: not significant, PGE1 = prostaglandin E1. Bold indicates $p < 0.05$				

Table 3. Side effects during PGE1 treatment

Variables	Obstruction to systemic blood flow, n = 91	Obstruction to pulmonary blood flow, n = 102	Inadequate mixing, n = 42	Overall n=235	p
Respiratory Apneas	6(6.5)	7(6.9)	4(9.5)	17(7.2)	NS
Cardiac					NS
Bradycardia	2(2.2)	3(2.9)	2(4.7)	7(3)	
Tachycardia	1(1.1)	1(0.9)	-	2(0.8)	
Arrhythmia	-	-	-	-	
Hypotension	3(3.3)	4(3.9)	1(2.4)	8(3.4)	
Anuria	-	-	-	-	
Flushing/rash	2(2.2)	2(1.9)	1(2.4)	5(2.1)	
Edema	13(14.2)	15(14.7)	10(23.8)	38(16.1)	
Hyperthermia	12(13.2)	12(11.8)	7(16.6)	31(13.1)	NS
Neurological					NS
Jitteriness	3(3.3)	5(4.9)	2(4.7)	10(4)	
Seizures	1(1.1)	1(0.9)	-	2(0.8)	
Gastrointestinal					NS
Feeding intolerance	12(13.2)	10(9.9)	5(11.9)	27(11.4)	
Necrotizing enterocolitis	2(1.2)	1(0.9)	1(2.4)	4(1.6)	
Peritonitis	-	-	-	-	
Other					NS
Thrombocytopenia	3(3.3)	2(1.9)	2(4.7)	7(3)	
Hypoglycemia	2(2.2)	2(1.9)	1(2.4)	5(2.1)	
Hypomagnesemia	1(1.1)	-	1(2.4)	2(0.8)	
Sepsis	4(4.4)	7(6.9)	3(7.1)	14(5.9)	
n (%), median (IQR) NS: not significant					

treatment.

Edema was observed in thirty-eight cases (16.1%), hyperthermia in thirty-one cases (13.1%), gastrointestinal issues in thirty-one cases (13.1%), and apnea in seventeen cases (7.2%). The observed side effects in the cases are summarized in Table 3.

Discussion

This study evaluated the use of low-dose prostaglandin E1 and its potential effects in term newborns diagnosed with duct-dependent congenital heart disease in the pediatric cardiac surgery intensive care unit of a high-volume cardiac center. We found that prostaglandin E1 can be used at low doses; dose escalation may be required more frequently in systemic-dependent DD-CHD cases, and observed side effects may occur less frequently compared to high-dose protocols. Our study contributes to the literature as one of the limited studies providing insights into these characteristics.

Prostaglandin E1 is recommended as a temporary initial treatment for infants with isolated defects that restrict pulmonary blood flow. This treatment is used in infants with conditions that limit arterial-venous mixing and impede systemic circulation. It ensures the patency of the ductus arteriosus and maintains pulmonary and systemic circulation and oxygenation until appropriate surgical intervention can take place [10]. The policy for administering PGE1 therapy to newborns with duct-dependent congenital heart disease includes a regimen with an initial dose of PGE1 at 0.03-0.05 µg/kg/minute. This regimen, proposed by Doblec, should be combined with early pediatric cardiology consultation, as it has been shown to improve outcomes [11].

Kramer et al. examined various doses in 91 patients and reported on the efficacy and side effect profile. The authors used different starting and maintenance doses. As a result, they recommended an initial dose of 0.015 µg/kg/minute, but noted that patients with systemic obstruction may require higher doses. Most of these patients initially received a prostaglandin E1 dose of 0.01 µg/kg/minute, and inadequate mixing was present in more than half of this cohort [12].

Vari et al. evaluated 154 cases of duct-dependent congenital heart disease. They found that Prostaglandin E1 at a starting and maintenance dose of 0.01 µg/kg/minute was sufficient to maintain ductal patency in 83% of our cohort. The incidence of respiratory depression requiring mechanical ventilation was low and was typically seen in premature infants. They stated that low-dose (0.01 µg/kg/minute) Prostaglandin E1 initiated for critical congenital heart disease is a safe and effective treatment. They also noted that the dose escalation in cases with pulmonary obstruction was higher compared to the systemic and mixing groups [7].

Yucel et al. provided evidence that maintenance doses as low as 0.003-0.005 could maintain ductal patency. However, in their cohort of 95 patients, they noted that all patients were initiated at doses of 0.03 µg/kg/minute or higher, with an average starting dose of 0.065 µg/kg/minute. The authors also concluded that lesions with systemic obstruction may require higher doses [13].

In our study, ductal patency was maintained in 84% of our cases at doses of 0.003-0.005, similar to findings by Yücel and colleagues. Similarly, patients with systemic obstruction required a significantly higher dose escalation.

PGE1 treatment may be accompanied by multiple adverse effects. Under the current dosage scheme, there are many reports regarding the side effects of PGE1, and it has been shown that side effects increase with higher doses. Cucerea et al. administered an initial dose of PGE1 at 0.06-0.15 µg/kg/minute by continuous infusion in their series of 66 cases.

During PGE1 treatment, eleven infants (16.7%) had apnea attacks, five infants (7.5%) had convulsions, thirty-three (50%) had a fever, and forty-seven (71.2%) had leukocytosis (more than 20.000/mm³), and fifty-two (78.8%) had edema. Other complications possibly related to PGE1 therapy were listed as 25.8% had gastrointestinal intolerance, 45.5% had hypokalemia, and 63.6% had irritability. Additional complications like ectropion, cardiac arrest, and antral hyperplasia were recorded in fewer than 5% of the neonates [14].

Shlomai et al. reported apnea in 20.7% of cases, edema in 18.3%, hyperthermia in 18.3%, and gastrointestinal symptoms in 13.4% in their series of 82 cases using PGE1 at a dose of 0.05 µg/kg/minute (6). Talosi et al. recorded a 42% rate of apnea with a 14% rate of intubation due to respiratory depression in their study of 49 cases at initial doses between 0.025 and 0.05 µg/kg/minute [15].

In the series by Vari and colleagues, respiratory problems were observed in 28% of cases at a continuous dose of 0.01 µg/kg/minute. In 10 of these patients, the respiratory depression was transient and did not merit initiation of respiratory support, although four were started on caffeine [7].

In our study, a significant decrease in the incidence of side effects was observed with the administration of low-dose PGE1 compared to high-dose applications.

Limitations

The main limitations of this study include its retrospective nature, single-center design, and the limited number of cases. Additionally, in cases of complete transposition of the great arteries with limited interatrial communication, maintaining ductal patency may be insufficient to ensure hemodynamic stability.

Conclusion

The use of low-dose PGE1 has been effective in maintaining ductal patency in term newborns diagnosed with duct-dependent congenital heart disease. A decrease in PGE1 side effects has been observed compared to the rates reported in the literature.

Scientific Responsibility Statement

The authors declare that they are responsible for the article's scientific content, including study design, data collection, analysis and interpretation, writing, and some of the main line, or all of the preparation and scientific review of the contents, and approval of the final version of the article.

Animal and Human Rights Statement

All procedures performed in this study were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki Declaration and its later amendments or comparable ethical standards.

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Conflict of Interest

The authors declare that there is no conflict of interest.

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